Abdominal symptoms and cancer in the abdomen

Abdominal symptoms and cancer in the abdomen: prospective cohort study in European primary care

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Abstract

Background: Different abdominal symptoms may signal cancer, but their role is unclear.

Aim: To examine associations between abdominal symptoms and subsequent cancer diagnosed in the abdominal region.

Design and Setting: Prospective cohort study. Surgeries of 493 general practitioners (GPs) in Norway, Denmark, Sweden, Scotland, Belgium, the Netherlands.

Method: Over a 10-day period, GPs recorded consecutive consultations; where patients presented with pre-specified abdominal symptoms, additional data on non-specific symptoms and features of the consultation were noted. Eight months later, data on all cancer diagnoses among all study patients in the participating general practices were requested from the GPs.

Results: Consultations with 61802 patients were recorded. Malignancy was subsequently diagnosed in 511 patients (0.8%). Abdominal symptoms were recorded in 6264 (10.1%) patients.

Among patients with a new cancer in the abdomen, 175 patients were diagnosed within 6 months after consultation. In a multivariate model, the highest sex and age adjusted hazard ratio (HR) was for the single symptom 'Rectal bleeding' (HR 19.1, 95%CI 8.7-41.7). PPVs >3% were found for 'Hematuria, macroscopic', 'Rectal bleeding', 'Involuntary weight loss', with variations according to age and sex. The three symptoms describing irregular bleeding had particularly high specificity in relation to colorectal, uterine or bladder cancer.

Conclusion: A patient with undiagnosed cancer may present with symptoms or no symptoms. Irregular bleeding must always be explained. Abdominal pain occurs in all types of abdominal cancer. Several symptoms may signal colorectal cancer. The findings are important for how the GP can think and act to contribute to earlier diagnosis.

Keywords: General practice, early diagnosis, cancer, symptoms, proportional hazard model

How this fits in

A cancer patient can present with no classical signs or symptoms. If a patient presents with an abdominal symptom, different symptoms have varying levels of association with abdominal cancer.

Three symptoms relating to irregular bleeding are highly suspicious for a cancer diagnosis unless an alternative diagnosis can be confirmed.

Abdominal pain can be a presenting symptom for all types of cancers of the abdomen, common or less common. In a common cancer such as colorectal cancer, almost all the investigated symptoms are potentially relevant. Several combinations of symptoms may initiate a suspicion about cancer in the abdomen.

Introduction

About half of cancers are located within the abdominal cavity (1). Abdominal symptoms (such as pain or bloating) may be associated with cancer. In a previous article, we described a cohort where approximately 10% of adult patients, consecutively consulting in general practice in six north European countries, presented with abdominal symptoms. For almost 5% of symptomatic patients, the symptoms were associated with cancers in the abdomen (2).

GPs play an active role in the diagnostic process of the majority of cancer patients (3-5). In population studies and in clinical practice, the high frequency of abdominal symptoms contrasts with the relatively rare diagnosis of a cancer within the abdomen (6, 7). This can make appropriate referral to more specialised services challenging. Much of the recent primary care literature has concentrated on elucidating symptoms of more common cancers such as colorectal cancer (8, 9): this not only reflects the importance of these more frequently occurring cancers, but also the challenge of collecting sufficient numbers of patients with less common cancers. Therefore, in addition to studying specific cancers, it may be helpful to study all cancers located in one anatomical region that present with similar symptom clusters.

This second article based on our prospective patient cohort study focuses on new cancer diagnoses in the abdominal region, diagnosed within six months of the index consultation. The aim is to analyse the extent to which various abdominal symptoms are associated with new cancers of the abdomen, and hence, how predictive of such cancers are specific abdominal symptoms.

Method

Setting

Methods (including variables of interest, power calculations and data analysis techniques) have been previously described in detail (2). The study was carried out in primary care practices in Norway, Denmark, Sweden, the Netherlands, Belgium, and Scotland. Overall, 493 participating GPs were recruited through academic institutions active in The Cancer and Primary Care Research International Network (Ca-PRI) (10).

Initial registrations

Between 25 February 2011 and 27 July 2011, participating GPs registered consecutive consultations with patients 16 years of age and older, over ten working days. GPs recorded sex and date of birth for all patients, and selected abdominal symptoms (Appendix 1) if presented during the consultation. If abdominal symptoms were recorded, GPs were asked a further series of symptom-related questions, including non-specific symptoms selected from medical literature related to cancer.

Follow up

Participating GPs consented to provide data on all cancer diagnoses (new or recurring) that occurred after the consultation date for any of their recorded, consulting patients. Eight months after these consultations, each GP was asked to report all such patients on a standardized proforma (Appendix 1). It was reasoned that a cancer present during the initial consultation would usually have presented and been diagnosed within six months, supported for instance by a study on ovarian cancer (11). The interval is also short enough to increase the probability that a recorded symptom has something to do with the as yet undiagnosed cancer (12). With the additional two months before completed proformas were collected, we assumed that all hospital reports about cancers diagnosed during the six month interval had reached the GPs.

GPs used electronic records to identify patients and to provide anonymised information about those patients registered during the initial study period and diagnosed with cancer during the follow-up period, regardless of whether they had presented with symptoms during the initial survey. Sex, date of birth, GP identifier and date of consultation were used for identifying the patients. Two reminders were sent to GPs. The last patient reported with cancer was diagnosed in April 2012.

We distinguished between ‘abdominal’ and ‘non-abdominal’ types of cancer. In the abdominal group we included all cancers of digestive organs, female genital organs (except cancer of the vulva) and urinary organs including testis. Carcinoids, lymphomas, soft tissue cancers, endocrine tumours and generalized, metastatic cancer were included if they showed any abdominal sign or symptom.

Data analysis

Statistical analyses were performed using SPSS, version 22, and STATA, version 14. The chi-square test was used to examine differences between groups. Association between symptoms and cancer has been expressed as Cox hazard ratio (HR), in addition to sensitivity/specificity and likelihood ratio (LR). Positive predictive value (PPV) is presented with age and sex subgroups. LR in our study expresses the likelihood of a symptom being present when cancer had been subsequently diagnosed, compared to absence of a cancer diagnosis at follow-up. HR expresses the hazard for cancer being diagnosed when a patient had presented a symptom, in relation to when no symptom had been presented. The reference group in our Cox analyses were patients without abdominal symptoms. Age was the time scale variable for Cox analyses; entry time was age at consultation and exit time was age at cancer or end of follow-up (30 April 2012). Age adjustment is thus inherent in the model. HR was calculated for single symptoms and for combinations of symptoms. In the multivariate analyses, HR was calculated in models where the most frequent symptoms and combinations of symptoms were adjusted for sex. Due to interaction we applied separate models for each symptom, and for the combination of symptoms. The proportional hazards assumption was not rejected for patients diagnosed within 180 days, nor was it rejected for all patients with new abdominal cancer. Sensitivity analyses for HR comprising the more numerous latter group were therefore additionally performed. Interaction analyses were also performed for age and each symptom; no such interactions were found. Cox analyses included only patients with a new cancer. Analyses presented in tables 2-4 include patients with new abdominal cancer diagnosed within 180 days after consultation and exclude all other cancer patients (Fig 1). Sensitivity analyses deal with all patients with new abdominal cancer and with all patients with new cancer.

Level of significance was 0.05.

Results

Patient profile and cancers detected

Sex and age of patients are shown in *Table 1*. After corrections for multiple consultations, 61802 patients were included in the cohort. Follow-up forms indicating 640 cancer patients were received from 315 GPs. After exclusions, 511 patients were included. Of 441 patients with a new cancer, 251 (56.9%) had abdominal and 190 non-abdominal cancers. Of these 251, 175 patients were diagnosed within six months of their GP consultation. Results presented in

this paper focus on these 175 patients (*Fig 1*). The higher proportion of males in relation to females in the group with abdominal cancers (P<0.001) was consistent with Norwegian population based data (1).

Profile of symptoms

Table 2 shows that of 175 patients with new abdominal cancer diagnosed within 6 months, 76 (43.4%) had abdominal symptoms and 39 (22.3%) had multiple abdominal symptoms. For patients with no cancer, 10.0% had abdominal symptoms and 4.5% multiple abdominal symptoms. Patients with new non-abdominal cancer had abdominal symptoms in 12.6% of cases, not different from patients without cancer.

Non-specific symptoms in patients with abdominal symptoms occurred in 29 (38.2%) of 76 cancer patients *(Table 2)*, and in 24.6% of patients with no cancer. Between patients with abdominal and non-abdominal types of cancer there was no significant difference in the recording of non-specific symptoms.

Measures of association and predictive value of abdominal symptoms in relation to new abdominal cancer

For the 175 patients with new abdominal cancer diagnosed within six months, table 2 shows the degree of association with cancer for each symptom, expressed as LR, sensitivity and specificity, and diagnostic probability expressed as positive predictive value (PPV) of symptoms. LR was slightly higher for females than males for most symptoms. Any abdominal symptom had a sensitivity of 43.4%, and more than one abdominal symptom 22.3%. The three symptoms indicating irregular bleeding, i.e. 'Rectal bleeding', 'Unexpected genital bleeding' and 'Hematuria, macroscopic' had higher specificity than the other symptoms, ranging from 99.4 to 99.8%.

Three symptoms reached the cancer referral guideline PPV threshold of 3% in England (13): 'Hematuria, macroscopic' 'Rectal bleeding' and 'Involuntary weight loss'. In the oldest age groups, several symptoms reached this threshold. The highest PPVs were for 'Unexpected genital bleeding' 8.1% in age group 55-74 years, and 'Hematuria, macroscopic' 7.9% for patients ≥75 years of age.

Table 3 shows hazard ratios for all single symptoms investigated in a multivariate model with patients without symptoms as reference group, i.e. 'Abdominal pain, upper part', 'Abdominal pain, lower part', 'Constipation', 'Rectal bleeding', and also for the variable gathering the remaining single symptoms being investigated. The highest HR for a single

symptom was for ‘Rectal bleeding’ (HR 19.1, 95% CI 8.7-41.7). For the combination of three or more abdominal symptoms HR was 14.0 (9.1-21.6). HR for males was 1.8 (1.4-2.5), - that is, if symptoms were recorded, the probability of cancer was higher in males.

Table 4 shows HR for different combinations of symptoms. The reference group is patients without symptoms. HR is shown for combinations of two symptoms, regardless of whether there were additional symptoms. The highest HR was for all combination categories containing ‘abdominal pain, upper part’ + ‘rectal bleeding’, HR 64.2 (26.9-153.1).

Table 5 shows the distribution of recorded symptoms for the main types of new abdominal cancers. The proportion of symptomatic cases varies for different cancers; there is a considerable variety of symptoms for most cancers, most pronounced in colorectal cancer. Abdominal pain was present in all individual cancer types. The three irregular bleeding symptoms were notable in that they each related strongly to cancer in one type of organ: Of 15 cancer patients with ‘Rectal bleeding’, 14 had either colon or rectal cancer. Of three cancer patients with ‘Unexpected genital bleeding’, two had uterine body and one cervical cancer. Of six cancer patients with ‘Hematuria, macroscopic’, three had bladder and one renal cancer. Altogether, 20 of the 24 cancer patients with irregular bleeding had cancers typically associated with such bleeding. This degree of specificity was not observed for other symptoms; for example, only six of 16 cancer patients with ‘Constipation’ and six of 20 cancer patients with ‘Abdominal pain, lower part’ had colon cancer,

Discussion

Summary

Abdominal symptoms were associated with new cancer in the abdominal region – the strength of these associations confirms the importance of responding appropriately to abdominal symptoms presenting in primary care (14-16). Conversely, a high proportion of new cancer diagnoses in the abdomen (56.6 %) did not feature such symptoms during consultations in the months before diagnosis. This duality underlines the need for a high index of suspicion and use of clinical judgement, in all phases of an illness episode. Symptoms are important, but on their own have insufficient sensitivity and specificity to underpin cancer diagnostic decisions. The diagnostic importance of PPV is considerable: ‘low’ values can still prompt action, illustrated by the lowering to the 3% threshold in the 2015 update of English referral guidelines (13), and additional information can increase or decrease the contribution to PPV

from a symptom (17-19). This is illustrated by the higher PPVs for certain symptoms in higher age groups.

Our study also provides important information on the relative significance of different types of symptoms, with high HR for 'Rectal bleeding' as a single symptom and the three 'bleeding' symptoms showing high specificity for certain types of cancer. Also, the broad range of cancers affected by abdominal pain and the variety of symptoms in colorectal cancer are important findings. Three or more abdominal symptoms increased the probability of cancer, and so did several other combinations of symptoms, especially 'abdominal pain, upper part' and 'rectal bleeding', as well as combinations of 'abdominal pain, upper part' and a non-specific symptom. Symptoms related to sex-specific types of cancer, like ovarian cancer and prostatic cancer, could be part of the explanation for sex differences. However, both these cancers were relatively symptom-poor in another study with cross-sectional registration before diagnosis (20). The higher proportion of abdominal cancer in males is largely due to the high number of prostate cancers, and the fact that the most common female cancer, breast cancer, is not within the abdominal cavity.

Strength and limitations

The prospective nature of the follow-up ensured that neither the patient nor the GP knew about the cancer diagnosis at the time of symptom registration, reducing the risk of bias inherent in retrospective studies. However, symptoms presenting before diagnosis but after the initial consultation do not show in the cross-sectional data from the consultations. Consecutive patients were registered, with no selection bias; all common abdominal symptoms were investigated.

We believe hazard ratios give a complex, but also a rather complete and precise estimate of the association between symptom and cancer. Sensitivity analyses for all 251 patients with a new abdominal cancer (including those whose cancers were diagnosed > 6 months after the consultation), gave HRs slightly lower than in tables 3-4. This gives support to the assumption that symptoms recorded more than six months before diagnosis may be less related to the subsequent cancer. Sensitivity analyses of all new cancer patients consistently gave slightly higher or lower HR in the expected direction, increasing the reliability of the estimates.

Comparison with existing literature

It has been shown previously that abdominal symptoms commonly precede diagnoses of abdominal cancers (15, 20). Our study provides a more detailed description of different symptoms located in the abdominal region. Such symptoms should alert clinicians to the possibility of abdominal cancers, without forgetting that they also may act as lower risk symptoms (21) in relation to other cancers.

Higher risk of cancer in men with symptoms as compared to women with similar symptoms, and the cumulative effect of multiple symptoms, are consistent with findings in a primary care-based, colorectal cancer study by Lawrenson et al (22). Hippisley-Cox & Coupland (9, 23) also used a large primary-care database and included information from the medical history and anemia in addition to combining different abdominal symptoms, constructing diagnostic algorithms. They analysed hazard ratio and found values not unlike ours, with especially high values for hematuria in relation to renal tract cancer, and rectal bleeding in relation to colorectal cancer.

Some of the symptoms we studied have been shown in previous studies to have higher PPV for specified types of cancer (24, 25), also for specific age groups, consistent with our findings. GP knowledge about PPV values may have an impact on reducing variation in referral threshold (26). Colorectal cancer is common and has been studied in primary care more than most other types of cancer. Hamilton (21, 27) found that less than half of colorectal cancer patients experienced rectal bleeding and emphasized the important role of 'low-risk-but-not-no-risk' symptoms, which are typically less likely to be referred to 'fast track' diagnosis. Non-specific symptoms have been shown to be associated with rectal bleeding in colorectal cancer patients (28), and this was the case for several of the patients with rectal bleeding and colorectal cancer in our study. A study from Sweden found that rectal bleeding combined with either diarrhea, constipation, change in bowel habit or abdominal pain are predictors of non-metastatic colorectal cancer, confirming that GPs have an opportunity window where they can make a difference for patient prognosis (29).

Non-specific symptoms have shown poor association with cancer if occurring alone (30), but their cancer-diagnostic importance increased if they occurred in combination with alarm symptoms. Our findings agree with this.

Several studies of the relationship between symptoms and cancer have used a longer observation period, commonly 12 (22) or 24 (9) months . Our reasons for choosing six months have been explained in the 'Method' section, and the sensitivity analyses performed seem to suggest that this was a wise approach, giving more precise HRs.

Implications for research and practice

A patient with abdominal cancer can present in a range of ways – they may be asymptomatic, or they may have multiple symptoms. Almost all reasons for encounter require further questioning and examination before the GP may suspect cancer and refer appropriately. Our study is relevant for a 'real life' consultation in primary care, at a time when abdominal symptoms can point to many kinds of illness.

All investigated symptoms in our study were associated with an abdominal cancer, however, different symptoms were related to cancer in different ways. The three 'bleeding' symptoms had particularly high specificity for the individual cancer type most associated with that symptom. Any of the three irregular bleeding symptoms should therefore lead to further investigation or referral unless a benign cause can be demonstrated. Even then, bleeding hemorrhoids do not exclude a more proximal cancer or polyp, and urinary infection with hematuria may mask bladder cancer.

Abdominal pain as a presenting symptom showed sensitivity for both common and less common types of abdominal cancer and should not be ignored, in spite of lower specificity than other symptoms. For colorectal cancer, almost all investigated symptoms warrant investigation. Several combinations of symptoms call for increased vigilance of GPs. Our study adds further prospective data to inform cancer diagnostic processes in primary care, and they encourage continued primary care research about symptoms and cancer.

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Ethical approval

The Regional Committee for Medical and health Research Ethics of Northern Norway approved the survey protocol (Ref 2010/1056-4). Ethical approval was thereafter given also in the other five participating countries. No patients were contacted. Only the individual GP knew the identity of the patient.

Competing interests: None of the authors declares any conflict of interest.

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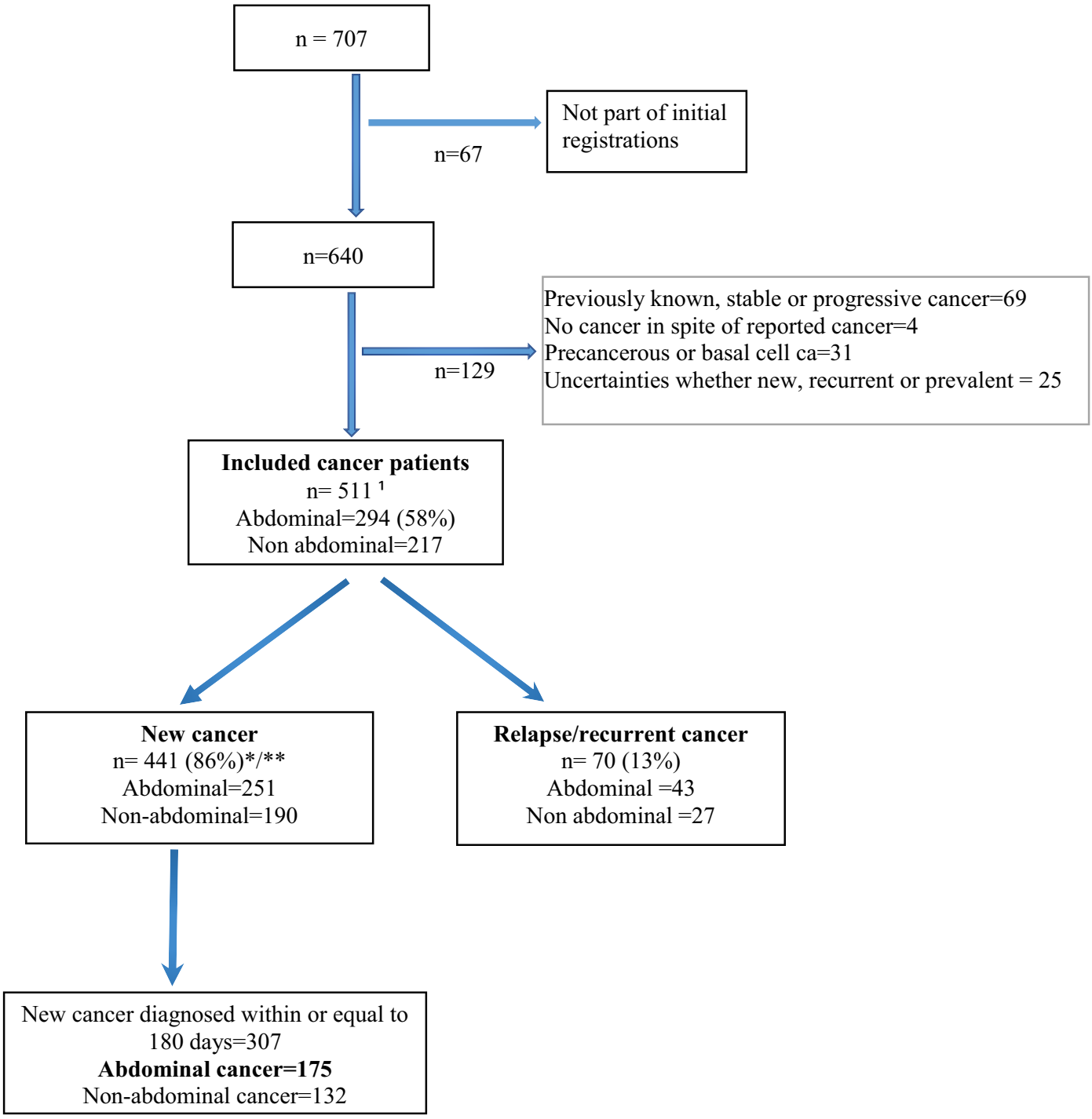
Figure 1: Inclusion and exclusion of patients with cancer



*One patient had two new cancers, colon cancer (counted here) plus squamous cell carcinoma of lung discovered in hospital. Lung cancer discovered incidentally during work-up.
**One patient had one new (prostate) and one recurrent (bladder) cancer. The prostate cancer has been counted here, because this was the new cancer.
¹ Most patients had a histological verification. The few remaining patients had other convincing evidence of cancer

Table 1: Number of patients : all patients, patients with symptoms and patients diagnosed with new cancer after consultation, by sex and different age groups. Mean/median age.

Age in years	16-29	%	30-54	%	55-74	%	≥75	%	Total	Mean	Median	Range	25-75 percentile
All patients	8457	14	23144	37	19983	32	10218	17	61802	53	54	16-102	38-68
Males	2931	12	8365	35	8689	36	3943	17	23928	55	56	16-102	41-69
Females	5526	15	14779	39	11294	30	6275	16	37874	53	52	16-101	37-68
Patients with symptoms	907	14	2261	36	1992	32	1104	18	6264	54	53	16-100	38-70
Males	236	11	767	35	792	36	401	18	2196	56	57	16-100	42-70
Females	671	16	1494	37	1200	30	703	17	4068	53	52	16-100	36-69
Patients with new cancer	2	1	71	14	221	43	217	42	441	69	71	28-96	60-80
Males	0	0	26	11	104	46	101	43	200	70	71	35-94	62-79
Females	2	1	45	16	117	42	116	41	241	69	70	28-96	59-80
Patients with new cancer, diagnosed within 6 months	2	1	47	15	130	42	128	42	307	69	71	28-96	59-80
Males	0	0	21	15	61	44	58	41	140	69	72	35-94	60-79
Females	2	1	26	16	69	41	70	42	167	69	71	28-96	59-80
Patients with new abdominal cancer, diagnosed within 6 months	1	1	23	13	74	42	77	44	175	70	73	28-96	60-80
Males	0	0	12	13	43	45	40	42	95	70	72	42-94	59-79
Females	1	1	11	14	31	39	37	46	80	70	74	28-96	61-81

Table 2. Association between symptoms and new abdominal cancer for 175 patients diagnosed within six months after consultation, expressed as likelihood ratio (LR), sensitivity, specificity, for all patients.
Also, diagnostic probability expressed as positive predictive value (PPV). LR and PPV with sex subgroups and PPV with age groups. LR, sensitivity and PPV with 95% confidence interval (CI) for all patients. N=61337 patients.

	Cancer Patients				Measures of association							Diagnostic probability (PPV)						
	All	Males	Females	No cancer	All		Males	Females	All		All	All		Males	Females	≤54 years	55-74 years	≥75 years
	N=175	N=95	N=80	N=61162	LR	95% CI	LR	LR	Sensitivity	95% CI	Specificity	PPV (%)	95% CI	PPV (%)	PPV (%)	PPV (%)	PPV (%)	PPV (%)
Abdominal symptoms																		
Abdominal pain, upper part	31	15	16	2046	5.3	3.8-7.4	5.2	5.7	17.7	12.4-24.2	96.7	1.5	1.0-2.1	2.0	1.2	0.8	1.7	3.8
Abdominal pain, lower part	20	8	12	2084	3.4	2.2-5.1	3.1	3.9	11.4	7.1-17.1	96.6	1.0	0.6-1.5	1.2	0.8	0.3	1.4	2.3
Constipation	16	6	10	676	8.2	5.1-13.2	7.2	10.0	9.1	5.3- 14.4	98.9	2.3	1.3-3.7	2.8	2.1	1.0	3.0	3.8
Diarrhea	8	3	5	1103	2.5	1.3-5.0	1.7	3.5	4.6	2.0-8.8	98.2	0.7	0.3-1.4	0.7	0.7	0.7	0.3	1.7
Distended abdomen, bloating	17	8	9	1011	5.9	3.7-9.3	5.7	6.4	9.7	5.8-15.1	98.3	1.7	1.0-2.6	2.2	1.3	1.3	1.2	3.9
Increased belching, flatulence	9	5	4	489	6.4	3.4-12.2	7.1	6.0	5.1	2.4-9.5	99.2	1.8	0.8-3.4	2.8	1.3	2.4	1.1	1.4
Acid regurgitation	10	5	5	669	5.2	2.9-9.6	5.3	5.4	5.7	2.8-10.3	98.9	1.5	0.7-2.7	2.1	1.1	0.9	2.6	1.1
Rectal bleeding	15	4	11	385	13.6	8.3-22.3	6.8	21.6	8.6	4.9-13.7	99.4	3.8	2.1-6.0	2.7	4.4	2.1	4.5	6.8
Unexpected genital bleeding	3	0	3	195	5.4	1.7-16.7	-	7.7	1.7	0.4-4.9	99.7	1.5	0.3-4.4	-	1.6	-	8.1	-
Hematuria, macroscopic	6	4	2	141	15.7	6.8-34.5	13.1	14.4	3.4	1.3-7.3	99.8	4.1	1.5-8.7	5.0	3.0	-	5.2	7.9
Increased urinary frequency	10	6	4	732	4.8	2.6-8.8	6.2	3.8	5.8	2.8-10.3	98.8	1.3	0.6-2.5	2.4	0.8	-	1.6	3.3
Other abdominal problems	18	9	9	1116	5.6	3.6-8.8	5.7	5.8	10.3	6.2-15.8	98.2	1.6	0.9-2.5	2.2	1.2	0.3	2.0	4.4
One symptom only	37	14	23	3354														
More than one abdominal symptom	39	19	20	2748	5	3.8-6.6	5.2	5.1	22.3	16.4-29.2	95.5	1.4	1.0-1.9	2.0	1.1	0.6	1.9	3.1
Any abdominal symptom	76	33	43	6102	4.4	3.7-5.2	3.9	5.1	43.4	36.0-51.1	90.0	1.2	1.0-1.5	1.5	1.1	0.3	1.6	3.2
No symptom	99			55060														
Non-specific symptoms, given at least one abdominal symptom																		
Lack of appetite	18	6	12	853	7.4	4.7-11.5	4.8	10.4	10.3	6.2-15.8	98.6	2.1	1.2-3.2	1.9	2.2	0.9	2.9	3.7
Unusual tiredness	17	5	12	812	7.3	4.6-11.6	4.9	10.1	9.7	5.8-15.1	98.7	2.1	1.2-3.3	1.9	2.1	1.1	1.6	4.6
Involuntary weight loss	11	5	6	304	12.7	7.1-22.7	10.9	14.8	6.3	3.2-11.0	99.5	3.5	1.8-6.2	4.2	3.1	2.0	0.9	7.8
More than one non-specific symptom	13	4	9	381	11.6	6.8-19.7	7.4	17.1	7.4	4.0-12.4	99.4	3.3	1.8-5.6	2.9	3.5	2.0	1.7	6.6
Any non-specific symptom	29	10	19	1500	6.8	4.8-9.5	4.9	9.0	16.6	11.4-22.9	97.5	1.9	1.3-2.7	1.9	1.9	0.7	2.2	4.2

Table 3. Number of patients, and sex and age adjusted hazard ratio (HR) for some important abdominal symptoms in relation to new abdominal cancer, diagnosed within 6 months after consultation. Multivariate Cox analysis with mutually exclusive groups *. Patients without symptoms as reference group. HR is shown for single symptoms and for multiple symptoms, regardless of whether there also were non-specific symptoms . N = 61337 patients

Symptoms	New abd cancer diagnosed within 6 months N=175	Males N=95	Females N=80	No cancer N=61162	HR	95% CI	HR males	HR females
Model with groups without overlap:								
No abdominal symptoms	99	62	37	55060	1.0	Ref.	1.0	1.0
Abdominal pain upper part, as single symptom	5	1	4	663	4.8	1.9-11.8	1.9	8.5
Abdominal pain lower part, as single symptom	5	2	3	608	5.8	2.4-14.3	3.8	9.1
Constipation, as single symptom	3	0	3	141	6.8	2.1-21.8		17.3
Rectal Bleeding, as single symptom	7	0	7	191	19.1	8.7-41.7		49.5
Any other single abdominal symptoms, grouped together	17	11	6	1751	4.7	2.8-7.9	4.9	4.3
Two abdominal symptoms	12	8	4	1574	4.6	2.5-8.5	5.6	3.5
Three or more abdominal symptoms	27	11	16	1174	14.0	9.1-21.6	10.2	21.1
Male sex		95	80		1.8	1.4-2.5		

* The model includes mutually exclusive groups (i.e. with no overlap, one patient cannot be part of more than one group) containing selected single symptoms, any other remaining symptoms grouped together, combinations of two symptoms, and of three or more symptoms.

Table 4. Number of patients and sex adjusted hazard ratio (HR) * for the most important combinations of two symptoms, with or without additional symptoms. Multivariate Cox analyses, with each row representing one separate model. Patients without symptoms as reference group. N = 61337 patients

Symptom combinations	New abd cancer diagnosed within 6 months N=175	Males N=90	Females N=85	No cancer N=61162	HR	95% CI	HR Males	HR Females
No abdominal symptoms	99	62	37	55060	1.0	Ref.	1.0	1.0
Abdominal pain upper part + lower part	7	3	4	543	8.1	3.7-17.6	6.7	11.1
Abdominal pain upper part + constipation	7	4	3	194	22.2	10.1-48.5	19.8	26.1
Abdominal pain upper part + diarrhea	5	3	2	361	11.5	4.6-28.8	17.6	8.8
Abdominal pain upper part + distended abdomen	11	5	6	458	15.0	8.0-28.3	12.4	19.9
Abdominal pain upper part + increased belching	9	5	4	263	23.2	11.4-46.7	21.1	26.1
Abdominal pain upper part + acid regurgitations	8	4	4	440	13.3	6.3-27.6	16.6	12.9
Abdominal pain upper part + rectal bleeding	6	3	3	47	64.2	26.9-153.1	57.5	100.5
Abdominal pain upper part + other abdominal problem	7	3	4	200	22.3	10.2-48.8	19.6	24.2
Abdominal pain lower part + constipation	7	3	4	296	12.6	5.8-27.5	9.2	19.7
Abdominal pain lower part + distended abdomen	6	3	3	449	7.9	3.4-18.0	7.1	9.6
Abdominal pain upper part + lack of appetite	14	6	8	457	17.2	9.7-30.5	14.9	22.4
Abdominal pain upper part + unusual tirednesss	10	4	6	342	16.8	8.6-32.8	13.4	23.3
Abdominal pain upper part + unexpected weight loss	5	3	2	130	21.6	8.6-54.2	30.8	18.2

* Criteria for analyses: All combinations with at least 50 patients presenting the combination, and at least 5 cases of cancer with that combination

Table 5. Number of symptoms recorded at consultation in the main types of new abdominal cancer, diagnosed within 6 months after consultation

Ca = Cancer

	Cancer patients	Oesophagal ca	Stomach ca	Pancreatic ca	Primary hepatic ca	Biliary ca	Colon ca	Rectal ca	Cervical ca	Uterine body ca	Ovarian ca	Renal ca	Bladder ca	Prostate ca
Number of patients	175	5	6	9	7	3	37	17	6	8	4	12	17	34
Hereof number of patients with symptom(s) recorded at consultation	76 *	3	5	2	3	1	22	12	2	3	3	4	4	8
Abdominal symptoms														
Abdominal pain, upper part	31	2	4	2	1	1	7	5	1		1	2		2
Abdominal pain, lower part	20		1				6	3		1	1	2	1	2
Constipation	16		1	1			6	4				1		1
Diarrhea	8						4	2		1				
Distended abdomen, bloating	17			1	2		6	4			1	1		
Increased belching, flatulence	9	1	2	1			2	2				1		
Acid regurgitation	10	2	1				1	4				1		1
Rectal bleeding	15		1				8	6						
Unexpected genital bleeding	3								1	2				
Hematuria, macroscopic	6									1		1	3	
Increased urinary frequency	10				1		1	1		1			2	3
Other abdominal problems	18	3	3		2		5				1		1	2
Non-specific symptoms, given at least one abdominal symptom														
Lack of appetite	18		2	1	1	1	4	2		1		1		
Unusual tiredness	17		2	1	1	1	5	2		1	1	2		
Involuntary weight loss	11		1	1		1	3	2			1		1	

* The total number of patients in this column is for some symptoms slightly higher than the sum of the other columns, because a few rare or more undetermined types of abdominal cancer have not been included in the table